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MITCHELL, LAURA MCGILLEM	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/524,399	KRAUSE ET AL.	
	Examiner	Art Unit	
	Laura M. Mitchell	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/11/2005, 5/17/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-3, 6 and 8-11) in the reply filed on 11/14/2008 is acknowledged. Election was made **without** traverse in the reply filed on 11/14/2008. On further consideration, the restriction requirement is withdrawn. It is noted that claims 4, 6-7, 8 and 10-11 are amended and claims 12-14 are canceled in the amendment filed 11/14/2008. Claims 1-11 are under examination.

Priority

It is noted that the instant Application is a National Stage of PCT/EP03/09292, filed 8/21/2003 and claims priority benefit of U.S. Provisional Patent Application No. 60/405,225, filed 8/22/2002. It is noted that embodiments of the invention such as use of a compound to treat CR (paragraphs 0033-0035 and 0010-0012) and specific genes that have been found to be differentially modulated listed in Tables 1-3 (paragraphs 0007-0008 and 0010-0012) are not supported in U.S. Provisional Patent Application No. 60/405,225. Therefore, claims 4-5 and 7 will be given priority benefit of only the filing date of the PCT/EP03/09292, 8/21/2003. Claims 1-3, 6 and 8-11 will receive priority benefit of U.S. Provisional Patent Application No. 60/405,225, filed 8/22/2002

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 7 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is vague and indefinite because it recites multiple genes to be monitored that are identified only by GenBank Accession numbers and not the names of the genes. The specification does not provide the gene sequences associated with these GenBank Accession numbers and does not provide SEQ ID NOs for these genes. Since sequences can be updated over time in the GenBank database, the metes and bounds of the genes identified by the GenBank Accession numbers is not clear. The genes associated with the recited Accession numbers may not be as Applicants have intended at the time of filing.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the application coupled with information known

in the art without undue experimentation *United States v. Telectronics*, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) and include the following:

Scope of the claims. The early chronic rejection diagnosis method as claimed encompasses a large scope. The claims encompass the transplantation of any tissue including hair follicles, bone marrow, skin, kidney, heart, lung, etc. which is a very large genus of tissue to be transplanted. The claims encompass evaluation of the modulation of expression of any at least one gene that would be indicative of early chronic rejection (CR) of transplanted tissue, which is potentially a large number of genes. The method comprises comparison of gene expression levels of a transplant patient who is not known to develop chronic rejection, such as a syngeneic transplant, to a patient at risk of developing CR, such as an allogeneic transplant. This encompasses comparison of gene expression between two different patients which would encompass a very large genus of genes which may have differential expression.

Claim 3 encompasses an additional step of adding a chronic rejection inhibiting agent, which encompasses a very large genus of potential CR inhibiting agents. The claims encompass a method of treating, preventing, reducing or inhibiting chronic rejection with an identified agent that can modulate the activity, expression or synthesis of one or more differentially expressed gene. The claims encompass a very large genus

of possible inhibiting agents including small molecules, antibodies and drug compounds (see paragraph 0026).

Nature of the invention. The claimed method involves predictive diagnosis of organ transplant rejection using analysis of modulation of gene expression which is a complex and unpredictable aspect of molecular cell biology and medicine. The claimed method also involves identification of agents for prevention, inhibition, reduction or treatment of chronic rejection, which is a complex and unpredictable aspect of medicine. The claimed method also involves prevention, inhibition, reduction or treatment of chronic rejection which is a complex and unpredictable aspect of medicine.

State of the Art. Damrauer et al (J. Leuk. Biol. Feb. 2002, Vol. 71, pages 348-358) teach that accepted methods of clinical diagnosis of allograft rejection is done using histological analysis of biopsy specimens, but despite standardized criteria, it is apparent that there are different mechanisms of rejection based on different clinical courses and varying responses to anti-rejection therapy that are not differentiated by histological examination. Damrauer et al discuss methods of producing meaningful data from transcriptional analysis of transplant samples. Damrauer et al teach that a major challenge in immunobiology involves the interpretation of global responses in whole organisms. It is thought that assessment and interpretation of large databases of gene responses is necessary to address allograft rejection in terms of global responses. Damrauer et al teach that the optimal size of necessary and sufficient databases required to interpret *in vivo* biological responses has not been established. Although expression profiles of thousands of gene can be gathered using gene-chip mRNA

analysis protocols, perhaps only a small subset of gene information is sufficient for differentiation of complex biological responses (see page 48, left column, for example). Damrauer et al teach that while gene-chip analysis presents the possibility of serendipitous discoveries, many of the gathered data points involve gene profiles that are negative, unchanged or not relevant to the biological question. Damrauer et al teach that a possible solution to excess data that may confound results is to analyze expression of smaller groups of genes selected on the basis of some prior knowledge of relevant function (see page 348, right column, for example). Damrauer et al used clustering of genes with similar patterns of expression grouped by self organizing maps (SOM). Damrauer et al teach that the selection of only nine genes (e.g. one from each subset defined by the SOM) is sufficient to recapitulate the differentiation of the experimental sample groups produced by cluster analysis. Damrauer et al teach that their strategy successfully decreased the number of genes to be analyzed from a pool of thousands (see page 349, left column, 1st paragraph, for example). Damrauer et al suggest that clinical use of diagnostic criteria would be enhanced if lower numbers of genes would be adequate to differentiate unique rejection responses. Damrauer et al exemplify an "extreme case of selecting a single gene from each SOM" to total nine genes (see page 352, right column, 2nd full paragraph, for example). Damrauer et al conclude that the ability to reduce the amount of data necessary to differentiate rejection states using molecular profiles has important practical implications for the diagnosis of graft rejections and the development of individualized therapeutic regimens (see page 357, left column, 2nd paragraph, for example).

Unpredictability of the art. The unpredictability of the presently claimed methods is manifested in the ability of the up- or down-regulation of any particular gene or set of genes to be predictive of the likelihood of chronic transplant rejection. The specification pinpointed ~ten genes with modulated expressions over time in 17 transplant patients. An organ transplant is a significant medical procedure. For example, a kidney transplant comprises the addition of another kidney to the patient, as well as relevant medication. It is possible that detected changes in gene expression may have resulted from alleviation of the kidney disease symptoms that rendered the transplant necessary and return to normal kidney function, or alternatively in response to transplant related medication. Although many of the patients did develop chronic rejection, the specification has not sufficiently described a link between the changes in gene expression and diagnosis of rejection. While Damrauer et al demonstrate a similar transcriptional analysis method using the analyses of the differential expression of only nine genes, these were preselected genes based on background data. The ten genes disclosed in the instant specification (Table 3) as having the most significant differential expression patterns between control and at risk transplant subjects appear to be selected on the basis of large fold changes in expression level rather than specific functional significance to diagnosis of early rejection. As taught by Damrauer et al, some genes with altered expression may have gene profiles that are not relevant to the biological question. Therefore it is unpredictable whether comparison of the values of gene expression between a baseline and a sample allograft tissue biopsy would produce results that would be accurately indicative of early chronic rejection.

The unpredictability of a method comprising administration of a chronic rejection inhibiting agent is manifested in the ability of any particular agent to modulate gene expression that would be altered by onset of early transplant rejection, and for that modulation to inhibit the rejection process. It is unpredictable that the skilled artisan would be able to diagnosis or treat early chronic transplant rejection by determining changes in expression in any particular gene or set of genes without excessive trial and error experimentation.

Working examples. To identify potential prognostic markers, Applicants have performed random double blind group study of gene expression from seventeen kidney transplant patient renal biopsies taken at the time of transplantation, six months and twelve months after transplantation (see paragraph 0046). Applicants performed RNA amplification, followed by microarray hybridization and analysis. The specification discloses that one patient group developed chronic rejection after six months and another group did not develop chronic rejection. The microarray data revealed a change in expression of approximately ten genes in 15 of the 17 patients. The specification discloses that changes in expression of the set of "discriminator genes" in a biopsy taken at 12 months post- transplantation were able to predict development of chronic rejection in a patient at 18 months post-transplantation. The specification does not provide an example of the method where the baseline gene expression values are taken from a transplanted subject that is different from the transplanted subject at risk of rejection. The specification does not provide an example of the method where the transplant is any other type besides a kidney transplant. The specification does not

provide an example of the method where the tissue biopsy is taken from any other tissue other than renal tissue in a kidney transplant.

The specification does not provide an example of a method where a CR inhibiting agent is administered to a subject or the CR inhibiting agent adjusted for any reason. The method of claim 3 recites the phrase "adjusting the agent accordingly" after comparing the level of at least one gene expression from before agent administration to after administration. Although the agent is recited as a CR inhibiting agent, the claim does not place any limitation on how the agent is supposed to inhibit CR. There is no correlation between administration of the agent and changes in the at least one gene so that the skilled artisan would know how to "adjust the agent accordingly". As the claim is written, it encompasses adjusting the agent itself (e.g. structurally or chemically) or encompasses adjusting the dosage of the agent, but does not specifically recite what outcome the step of adjusting the agent is intended to produce in relation to gene expression. The specification does not provide any example of a method of preventing, inhibiting, reducing or treating chronic rejection in a transplant subject by administering a compound that modulates the synthesis or expression or activity of one more genes or gene products identified as differentially expressed in patients at risk of chronic allograft rejection. The specification does not provide any example of a method of identifying agents for prevention, inhibition, reduction or treatment of chronic rejection in a transplant subject comprising the step of monitoring the level of mRNA expression of one more genes or gene products identified as differentially expressed in patients at risk of chronic allograft rejection.

Amount of guidance provided. The specification does not provide any guidance regarding how gene expression in any other patient would meaningfully relate to the likelihood of transplant rejection in another individual. The specification discloses that the CR inhibitor can be a small molecule, an antibody or other therapeutic candidate agent that would be useful to change the level of expression of at least one gene to higher or lower levels than detected. The specification does not provide any specific guidance regarding what particular CR inhibitor might have an effect on any at least one modulated gene so that chronic rejection would be inhibited. The specification does not provide specific guidance regarding possible CR inhibiting agents including small molecules, antibodies and drug compounds (see paragraph 0026). The specification does not provide specific guidance regarding how to administer (i.e. dosage, or administration schedule) the CR inhibiting agents to a subject with the potential for developing early chronic rejection. Therefore, the skilled artisan would have to practice undue and excessive trial and error experimentation in order to make and use the claimed methods.

Level of skill in the art. Although the skill in the art is high, given the nature of the invention, the scope of the claims, state of the art, unpredictability of the art and lack of sufficient guidance and working example, the skilled artisan would have to practice undue and excessive trial and error experimentation in order to practice the claimed method.

Given the above analysis of the factors which the Courts have determined are critical in ascertaining whether a claimed invention is enabled, it must be considered

that the skilled artisan would have had to have practiced undue and excessive experimentation in order to practice the claimed invention.

Claims 1-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement for a genus may be satisfied by sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that applicant was in possession of the claimed invention.

Applicants claim a method of early diagnosing chronic rejection (CR) in a transplanted subject comprising a step pf comparison of mRNA expression between a subject not known to develop CR, with mRNA expression with a subject at risk for developing CR, wherein a first value lower or higher than the second value predicts that the transplanted subject is at risk of developing CR. Applicants claim a method of identifying CR inhibiting agents (claim 5). Applicants claim a method comprising administration of a CR inhibiting agent to a transplanted subject in order to optimize the CR inhibiting agent (claim 3) or to prevent, inhibit, reduce or treat CR by modulating the

synthesis, expression or activity of one of the genes identified as being differentially expressed between a subject at risk of developing CR (claim 4).

In the instant case, the specification discloses genes (Tables 1-2) that have been found to be differentially expressed between a subject at risk of developing CR for a kidney transplant and a control kidney transplant subject. The specification also discloses a subset of ten genes with the most significant differential expression patterns (see Table 3). The specification does not provide a correlation between the structure and identity of any one of the ten genes and their suggested function as indicators of early chronic rejection either individually or as a group. There is no description of mutational sites which naturally occur in the molecules and there is no description of how the structure of the disclosed ten genes relates to the structure of an indicator gene for transplant rejection. The genus of genus would be expected to have divergent functional properties. The applicant does not provide an indication of how the sequences of any one of the ten genes with the most significant differential expression patterns is representative of other genes that would change expression as an indicator of chronic rejection for any one type of organ transplant. The common attributes of the differentially expressed mRNA sequences are not described and the identifying attributes of the individual differentially expressed genes that are similar to the disclosed genes are not described. Therefore, there is not a structural and functional basis provided by the prior art or the specification for one of ordinary skill in the art to envision all differentially expressed genes that are indicative of early chronic transplant rejection.

In the instant case, the specification discloses only general embodiments of the CR inhibitor such as a small molecule, antibody or other therapeutic agent (see paragraph 0026) for the claimed CR inhibitor. The function of the inhibitor is disclosed as capable of modulating the synthesis, expression or activity of one of the genes identified as being differentially expressed between a subject at risk of developing CR and a control subject. The specification does not disclose any potential CR inhibitor that might be specific for any one of the ten significant genes disclosed in Table 3 so that the skilled artisan could envision a CR inhibitor to be used for methods to prevent, inhibit, reduce or treat chronic rejection, or monitor the effect of the CR inhibitor in order to adjust the agent as recited in claim 3. The common attributes of any recited CR inhibitors is not described. The applicant does not provide an indication of how the generally disclosed CR inhibitors types are representative of CR inhibitors with the function of preventing, inhibiting, reducing or treating chronic rejection. Therefore, there is not a structural and functional basis provided by the prior art or the specification for one of ordinary skill in the art to envision all CR inhibitors that are functional as therapeutics of any kind for early chronic transplant rejection. According to these facts, one of skill in the art would conclude that applicant was not in possession of the claimed genus because a description of only one member of this genus is not representative of the variant of the genus and is insufficient to support them.

Claim 7 is drawn to a method for identifying agents for treatment of chronic rejection comprising monitor the level of mRNA expression of one or more genes or

gene products wherein the genes are selected from a group of genes that are identified in the claim by GenBank Accession numbers only.

In the instant case, the specification discloses one GenBank Accession number for each gene that would have an altered level of mRNA expression during chronic rejection. The specification does not provide the gene sequences identified by SEQ ID NOs associated with these GenBank Accession numbers. Since sequences can be updated over time in the GenBank database, the genes associated with the recited Accession numbers may not be as Applicants have intended at the time of filing.

The genus would be expected to have divergent functional properties as small changes in sequence can have significant effects on the structure and properties of the gene or genes useful for monitoring alteration in mRNA expression during chronic early rejection. The applicant does not provide an indication of how the GenBank Accession numbers of any particular gene is representative of any sequence change in that gene that may have occurred before the filing date of the instant application. Therefore, there is not a structural and functional basis provided by the prior art or the specification for one of ordinary skill in the art to envision all gene sequences identified by a particular GenBank Accession number. According to these facts, one of skill in the art would conclude that applicant was not in possession of the claimed genus of sequences that might be represented by a particular GenBank Accession number because a description of only one member of this genus is not representative of the variant of the genus and is insufficient to support them.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-5 and 10-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Russell et al (US Patent No. 5,527,884, 6/18/1996).

Russell et al teach methods of analysis of gene expression corresponding with chronic allograft rejection of rat heart transplant. Russell et al teach the identification of transcriptionally regulated gene for rat hearts from a syngeneic transplantation and allogeneic transplantation (see column 11, lines 5-22, for example). Absent evidence to the contrary, a rat with a syngeneic transplant would meet the limitation of a transplanted subject who is known not to develop chronic rejection. A rat with allogeneic heart transplantation would meet the limitation of a subject at risk of developing chronic rejection. Russell et al used differential mRNA display and determined that twelve PCR products were differentially expressed between the allogenic and syngeneic tissue at 7- and 14-day post-transplantation (see column 11, lines 5-22, for example). Russell et al cloned and sequenced several PCR produced sequences and identified two unknown genes and three known genes not previously implicated in chronic rejection mechanisms. Russell et al teach that these selection methods are designed to identify mediators that would be specific for chronic rejection (see column 12, lines 46-65, for

example). Therefore Russell et al meet the limitation of early diagnosis of chronic rejection (**claim 1**).

Russell et al teach that Gal/GalNAc macrophage lectin has been first identified by this assay as having a possible role in pathogenic state-chronic cardiac rejection (see column 19, lines 10-25, for example). Russell et al suggest that allograft rejection could be inhibited by addition of inhibitors that block the interaction of the Gal/GalNAc lectin to Gal/GalNAc. Russell et al teach an assay in which an organ to be allografted can be contacted with a solution containing a candidate inhibitor compound prior to transplantation, and then the organ can be transplanted into the subject. It is routine procedure in the art in any screening method to take a control or baseline measurement in order to compare it to sample measurements. Therefore, the skilled artisan would know to obtain a sample of transplant tissue before contacting the organ with the CR inhibiting agent and detecting the level of mRNA corresponding to a differentially expressed gene, in order to be able to make a comparison with the post inhibitor agent sample. Russell et al teach that a tissue biopsy can be evaluated for differential expression of an allograft gene such as Gal/GalNAc lectin (see column 25, lines 1-14, for example), which meets the limitation of a step of obtaining a sample of transplant tissue post-administration of a CR inhibiting agent, detecting the level of mRNA corresponding to a differentially expressed gene.

Russell et al teach that peptide analogs are embodiments of a CR inhibition compound. Russell et al teach that analogs of proteins encoded by differentially expressing genes can comprise conservative amino acid replacements that do not

affect the function of the peptide. Russell et al teach that modifications to an analog peptide include changes in post-translational modifications such as glycosylation. Russell et al teach that where proteolytic degradation of a peptide is an issue, replacement of a sensitive peptide with a non-cleavable peptide will stabilize the peptide and make it more useful as a therapeutic (see column 25, lines 59-67, for example), which meets the limitation of a method step of adjusting a CR inhibiting agent accordingly. Therefore Russell et al meet the limitation of **claim 3**.

Russell et al teach that peptides or their analogs or mimetics can be administered to patients in a pharmaceutically acceptable carrier (see column 26, lines 11-15), which meets the limitation of administering a compound to a subject. Russell et al suggest that allograft rejection could be inhibited by addition of inhibitors that block the binding activity of the Gal/GalNAc lectin to Gal/GalNAc (see column 25, lines 10-20, for example), which meets the limitation of a compound that modulates the activity of a gene product identified as Gal/GalNAc lectin so that a symptom of chronic rejection would be alleviated (**claim 4**)

Claim 5 is drawn to a method for identifying agents for use in the prevention, inhibition, reduction or treatment of CR comprising monitoring the level of mRNA expression of one or more genes or gene product as identified in the method for determining differential expression of genes during chronic rejection. Identifying an inhibitor that blocks the interaction of the Gal/GalNAc lectin to Gal/GalNAc such as a peptide or peptide analog or mimetic also meets the limitation of **claim 5**.

Russell et al teach that mRNA analysis was done using Northern blotting protocols (see column 4, lines 11-20 and Figure 1B and Figure 3A, for example), which meets the limitation of a method wherein the level of mRNA expression is detected by Northern blot analysis (**claim 10**).

It is noted that claim 11 recites the limitation of "a set of genes" but does not provide a limiting definition of what constitutes "a set of genes", therefore it will be given the broadest reasonable interpretation. Since Russell et al teach that that some of the twelve genes that were differentially modulated are genes that were not identified previously or some genes that were not previously thought to be associated with allograft rejection. Therefore the rest of the twelve genes that were differentially modulated are genes that would be expected to be altered during chronic rejection, which meets the limitation of a "set of genes" and anticipates **claim 11**.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Russell et al (U.S. Patent No. 5,527,884, 6/18/1996) in view of Damrauer et al (J. Leuk. Biol. Feb. 2002, Vol. 71, pages 348-358).

Applicants claim a method of early diagnosing chronic rejection wherein the baseline value is obtained by detecting a level of mRNA expression corresponding to or protein encoded by at least one gene in an allograft tissue biopsy obtained from the donor at the day of transplantation.

The teaching of Russell et al is detailed in the rejection above. Specifically, Russell et al use differential mRNA display to examine mRNA expression and determined that twelve PCR products were differentially expressed between the allogenic and syngeneic tissue at 7- and 14-day post-transplantation (see column 11, lines 5-22, for example). Russell et al do not teach that the baseline was obtained from the donor at the day of transplantation.

Damrauer et al teach molecular profiles of murine heart allografts at risk for rejection. Damrauer et al teach that the transplants were from syngeneic and allogeneic donor hearts (see page 349, left column, 2nd paragraph, for example). Damrauer et al teach that mRNA was determined from donor grafts on day 0, 1, 3, 5 and 7 post transplantation (see page 349, right column, 3rd paragraph, for example), which meets the limitation of a biopsy obtained from the donor at the day of transplantation. Damrauer et al teach that the difference in mRNA expression resulting from days 1 and 3 (early), and days 5 and 7 (late) are clearly segregated and early samples show a lesser degree of dissimilarity with comparative samples (see page 350, left column, and page 351, left column, for example)

It would have been obvious to the skilled artisan at the time of the invention to modify the method taught by Russell et al of examining differential gene expression in

transplanted heart tissue at day 7- and 14-day post-transplantation and take a biopsy at day 0 and 1 of transplantation as taught by Damrauer et al because taking a tissue biopsy on the day of transplantation in addition to or instead of at day 7 post-transplantation amounts to routine optimization of the method. The motivation to take a baseline tissue biopsy at the day of transplantation is the expected benefit of being able to get an accurate baseline of mRNA expression before any rejection related changes occur. There is a reasonable expectation of success in being able to perform a differential mRNA expression analysis using a baseline sample from the day of transplantation because it has worked in the Damrauer et al reference. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore Russell et al in view of Damrauer et al render obvious method of early diagnosing chronic rejection wherein the baseline value is obtained by detecting a level of mRNA expression corresponding to or protein encoded by at least one gene in an allograft tissue biopsy obtained from a donor at the day of transplantation (**claim 2**).

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Russell et al (U.S. Patent No. 5,527,884, 6/18/1996) in view of Strehlau et al (PNAS, 1997, Vol. 94 pages 695-700).

Applicants claim a method of early diagnosing chronic rejection wherein the transplanted subject is a kidney transplanted subject.

The teaching of Russell et al is detailed in the rejection above. Russell et al teach methods of analysis of gene expression corresponding with chronic allograft rejection of rat heart transplant. Russell et al do not teach renal allograft rejection.

Strehlau et al teach an RT-PCR assay to test the diagnostic accuracy of an analysis of multiple immune activation gene analysis in order to diagnose renal allograft rejection. Strehlau et al examine expression of approximately fifteen immune activation genes in sixty renal allograft core biopsies (see page 695, abstract, for example). Strehlau et al teach that allograft rejection is a T-cell dependent process and may be associated with a specific subset of T cell dependent immune activation genes that may serve as a diagnostic indicator of rejection (see page 695, right column, 1st full paragraph, for example). Strehlau et al teach that loss of graft function due to acute and chronic rejection is a leading cause of end-stage renal failure (see page 695, left column, 1st full paragraph, for example).

Strehlau et al teach that current diagnostic procedures in renal allograft rejection depend on evidence of organ dysfunction and diagnosis of acute rejection must be made retrospectively on response to anti-rejection therapy. Strehlau et al hypothesized that clinical allograft rejection is associated with expression of specific subset of immune activation genes and subsequently determined that allograft rejection is associated with the expression of certain T cell dependent activation genes (see page 698, right column, 2nd paragraph, for example). Strehlau et al teach that using RT-PCR method allows the quantification of target genes within a few hours and provides a useful tool to diagnose acute rejection. Strehlau et al teach that a future challenge is to identify early

warning markers and use gene analysis to elucidate specific pattern in chronic rejections (see page 699, right column, 4th paragraph, for example).

It would have been obvious to the skilled artisan at the time of the invention to modify the method taught by Russell et al of examining differential gene expression in transplanted heart tissue and use the method on renal transplant subjects because Strehlau et al teach that allograft rejection is associated with the expression of certain T cell dependent activation genes. The motivation to use the method of Russell et al on renal transplant subjects to determine differential expression of genes between a baseline transplant subject and a chronic rejection risk transplant in order to be able to diagnose early chronic rejection is the expected benefit of being able to identify early warning markers and use gene analysis to elucidate specific pattern in chronic rejections of kidney transplants as is needed as taught by Strehlau et al (see page 699, right column, 4th paragraph, for example). There is a reasonable expectation of success in being able to practice the method of Russell et al with a kidney allograft tissue biopsy because Strehlau et al has already identified some candidate genes for analysis. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore, Russell et al in view of Strehlau et al render obvious a method of early diagnosing chronic rejection wherein the transplanted subject is a kidney transplanted subject (**claim 6**).

Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Russell et al (U.S. Patent No. 5,527,884, 6/18/1996) in view of Bennett et al (U.S. Patent No. 5,883,082, 4/16/1999).

Applicants claim a method of early diagnosing chronic rejection wherein the level of gene expression is assessed by detecting the presence of a protein corresponding to the gene expression product and wherein the protein is detected using a reagent that specifically binds to the protein.

The teaching of Russell et al is detailed in the rejection above. Russell et al do not teach that gene expression is measured by assessing presence of a protein.

Bennett et al teach compositions and methods for the prevention of allograft rejection including compositions that comprising antisense oligonucleotides targeted to sequences encoding cellular adhesion molecules (see column 1, lines 15-30). Bennett et al teach that the effect of antisense targeting of the adhesion molecules can be modulation of gene expression of the sequences encoding adhesion molecules. Bennett et al teach that modulation can be measured using methods which are routine in the art such as northern blot assay of mRNA expression or western blot assay of protein expression (see column 5, lines 16-25, for example). Bennett et al also teach method of using ELISA assays using specific monoclonal antibodies to detect changes in gene expression (see column 9, lines 15-25, for example).

It would be obvious to the skilled artisan at the time the invention was made to modify the method taught by Russell et al and determine differential expression of some genes associated with allograft rejection by detecting the presence of a protein encoded

by the transcript with a western blot in place of a step of differential mRNA expression with a northern blot or microarray because the methods are well known and routine in the art for determining expression and the substitution of one known element (i.e., protein detection with a western blot) for another (i.e. mRNA expression with a northern blot) would yield predictable results of determination of gene expression to the skilled artisan at the time the invention was made. There is a reasonable expectation of success to use protein detection to determine changes in gene expression because it has worked in the cited reference. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention. Therefore Russell et al in view of Bennett et al render obvious a method of early diagnosing chronic rejection wherein the level of gene expression is assessed by detecting the presence of a protein corresponding to the gene expression product (**claim 8**). Bennett et al also teach method of using ELISA assays using specific monoclonal antibodies to detect changes in gene expression (see column 9, lines 15-25, for example) which meets the limitation of a method wherein protein is detected using a reagent (i.e. monoclonal antibodies) that specifically bind to the protein (**claim 9**).

It is noted that this Office Action contains rejections of the same claims under 35 USC 112, 1st (enablement) and 35 USC 102 and 35 USC 103. While these rejections may seem contradictory, they are not, because each is based upon a different legal

analysis, i.e., sufficiency of the disclosure of the instant application to support claims under 35 USC, 1st paragraph vs. sufficiency of a prior art disclosure to anticipate or render obvious an embodiment(s) of the claimed invention (See *In re Hafner*, 161 USPQ 783(CCPA 1969)).

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to LAURA M. MITCHELL whose telephone number is (571)272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Laura M. Mitchell
Examiner
2/19/2008

/Celine X Qian Ph.D./
Primary Examiner, Art Unit 1636